Lyme disease

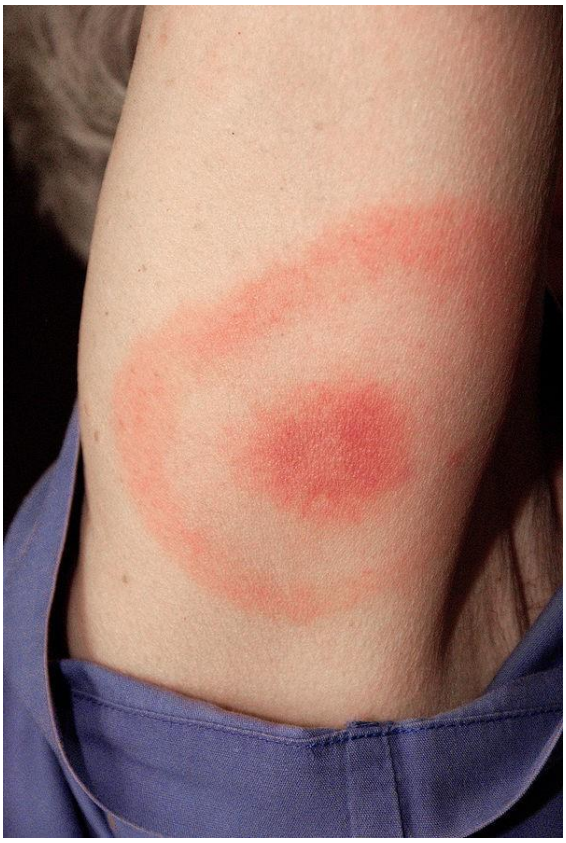
Lyme disease, also known as **Lyme borreliosis**, is an infectious disease caused by bacteria of the *Borrelia* type.[1] The most common sign of infection is an expanding area of redness, known as erythema migrans, that begins at the site of a tick bite about a week after it has occurred. The rash is typically neither itchy nor painful. About 25% of people do not develop a rash. Other early symptoms may include fever, headache, and feeling tired. If untreated, symptoms may include loss of the ability to move one or both sides of the face, joint pains, severe headaches with neck stiffness, or heart palpitations, among others. Months to years later, repeated episodes of joint pain and swelling may occur. Occasionally, people develop shooting pains or tingling in their arms and legs. Despite appropriate treatment, about 10 to 20% of people also develop joint pains, have memory problems, and feel tired much of the time.[2]

Lyme disease is transmitted to humans by the bite of infected ticks of the *Ixodes* genus.[3] Usually, the tick must be attached for 36 to 48 hours before the bacteria can spread.[4] In North America, the only bacterium involved is *Borrelia burgdorferi sensu stricto*, while in Europe and Asia, the bacteria *Borrelia afzelii* and *Borrelia garinii* are also causes of the disease.[1] The disease does not appear to be transmissible between people, by other animals, or through food.[4] Diagnosis is based upon a combination of symptoms, history of tick exposure, and possibly testing for specific antibodies in the blood.[5][6] Blood tests are often negative in the early stages of the disease.[1] Testing of individual ticks is not typically useful.[7]

Prevention includes efforts to prevent tick bites such as by wearing long pants and using DEET.[1] Using pesticides to reduce tick numbers may also be effective.[1] Ticks can be removed using tweezers.[8] If the removed tick was full of blood, a single dose of doxycycline may be used to prevent development of infection, but is not generally recommended since development of infection is rare.[1] If an infection develops, a number of antibiotics are effective, including doxycycline, amoxicillin, and cefuroxime.[1] Treatment is usually for two or three weeks.[1] Some people develop a fever and muscle and joint pains from treatment which may last for one or two days.[1] In those who develop persistent symptoms, long-term antibiotic therapy has not been found to be useful.[1][2]

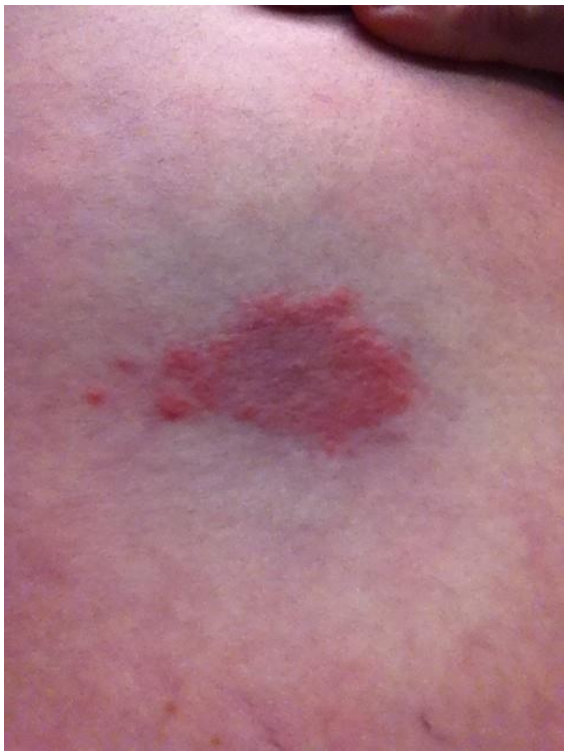
Lyme disease is the most common disease spread by ticks in the Northern Hemisphere.[9] It is estimated to affect 300,000 people a year in the United States and 65,000 people a year in Europe.[1][10] Infections are most common in the spring and early summer.[1] Lyme disease was diagnosed as a separate condition for the first time in 1975 in Old Lyme, Connecticut (it was originally mistaken for juvenile rheumatoid arthritis).[11] The bacterium involved was first described in 1981 by Willy Burgdorfer.[12] Chronic symptoms are well described and are known as post-treatment Lyme disease syndrome, although it is often called chronic Lyme disease. Some healthcare providers claim that it is due to ongoing infection; however, this is not believed to be true.[13] A previous vaccine is no longer available. Research is ongoing to develop new vaccines.[1]

1 Signs and symptoms



This "classic" bull's-eye rash is also called erythema migrans. A rash caused by Lyme does not always look like this. Around 20% to 30% of persons who are infected with Lyme disease may have no rash.[14][15]

Lyme disease can affect multiple body systems and produce a broad range of symptoms. Not all patients with Lyme disease have all symptoms, and many of the symp-



Raised, red borders around indurated central portion

toms are not specific to Lyme disease, but can occur with other diseases, as well. The incubation period from infection to the onset of symptoms is usually one to two weeks, but can be much shorter (days), or much longer (months
to years).[16]

Symptoms most often occur from May to September, because the nymphal stage of the tick is responsible for most cases.[16] Asymptomatic infection exists, but occurs in less than 7% of infected individuals in the United States.[17] Asymptomatic infection may be much more common among those infected in Europe.[18]

1.1 Early localized infection

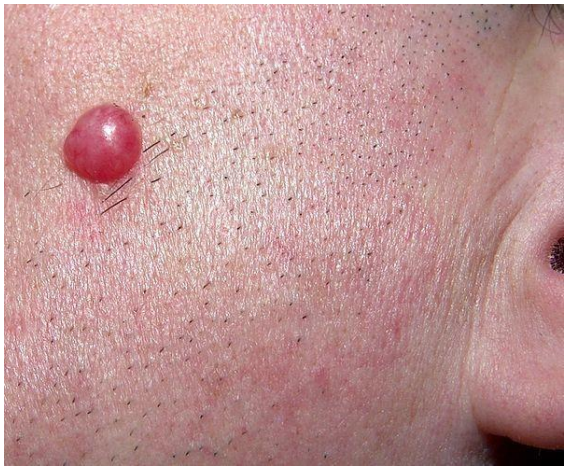
Early localized infection can occur when the infection has not yet spread throughout the body. Only the site where the infection has first come into contact with the skin is affected. The classic sign of early local infection with Lyme disease is a circular, outwardly expanding rash called erythema chronicum migrans (EM), which occurs at the site of the tick bite three to 32 days after the tick bite.[1] The rash is red, and may be warm, but is generally painless. Classically, the innermost portion remains dark red and becomes indurated (is thicker and firmer), the outer edge remains red, and the portion in between clears, giving the appearance of a bull's eye. However, partial clearing is uncommon, and the bull's-eye pattern more often involves central redness.[1]

The EM rash associated with early infection is found in about 80% of patients[1] and can have a range of ap*1 SIGNS AND SYMPTOMS*

pearances including the classic target bull's-eye lesion and nontarget appearing lesions. The 20% without the EM and the nontarget lesions can often cause misidentification of Lyme disease.[19] Affected individuals can also experience flu-like symptoms, such as headache, muscle soreness, fever, and malaise.[20] Lyme disease can progress to later stages even in patients who do not de-
velop a rash.[18][21]

1.2 Early disseminated infection

Within days to weeks after the onset of local infection, the *Borrelia* bacteria may begin to spread through the bloodstream. EM may develop at sites across the body that bear no relation to the original tick bite.[22] Another skin condition, apparently absent in North American patients, but found in Europe, is borrelial lymphocytoma, a purplish lump that develops on the ear lobe, nipple, or scrotum.[23] Other discrete symptoms include migrating pain in muscles, joints, and tendons, and dizziness.



Borrelial lymphocytoma on the cheek (very uncommon)

Various acute neurological problems, termed neuroborreliosis, appear in 10–15% of untreated patients.[20][24] These include facial palsy, which is the loss of muscle tone on one or both sides of the face, as well as meningitis, which involves severe headaches, neck stiffness, and sensitivity to light. Inflammation of the spinal cord's nerve roots can cause shooting pains that may interfere with sleep, as well as abnormal skin sensations. Mild encephalitis may lead to memory loss, sleep disturbances, or mood changes. In addition, some case reports have described altered mental status as the only symptom seen in a few cases of early neuroborreliosis.[25] The disease may adversely impact the heart's electrical conduction system and can cause abnormal heart rhythms such as atrioventricular block.[26]

1.3 Late disseminated infection

After several months, untreated or inadequately treated patients may go on to develop severe and chronic symptoms that affect many parts of the body, including the brain, nerves, eyes, joints, and heart. Many disabling symptoms can occur, including permanent impairment of motor or sensory function of the lower extremities in extreme cases.[18] The associated nerve pain radiating out from the spine is termed Bannwarth syndrome,[27] named after Alfred Bannwarth.

The late disseminated stage is where the infection has fully spread throughout the body. Chronic neurologic symptoms occur in up to 5% of untreated patients.[20] A polyneuropathy that involves shooting pains, numbness, and tingling in the hands or feet may develop. A neurologic syndrome called Lyme encephalopathy is associated with subtle cognitive difficulties, insomnia, a general sense of feeling unwell, and changes in personality.[28] Other problems, however, such as depression and fibromyalgia, are no more common in people with Lyme disease than in the general population.[29][30]

Chronic encephalomyelitis, which may be progressive, can involve cognitive impairment, brain fog, migraines, balance issues weakness in the legs, awkward gait, facial palsy, bladder problems, vertigo, and back pain. In rare cases, untreated Lyme disease may cause frank psychosis, which has been misdiagnosed as schizophrenia or bipolar disorder. Panic attacks and anxiety can occur; also, delusional behavior may be seen, including somatoform delusions, sometimes accompanied by a depersonalization or derealization syndrome, where the patients begin to feel detached from themselves or from reality.[31][32]

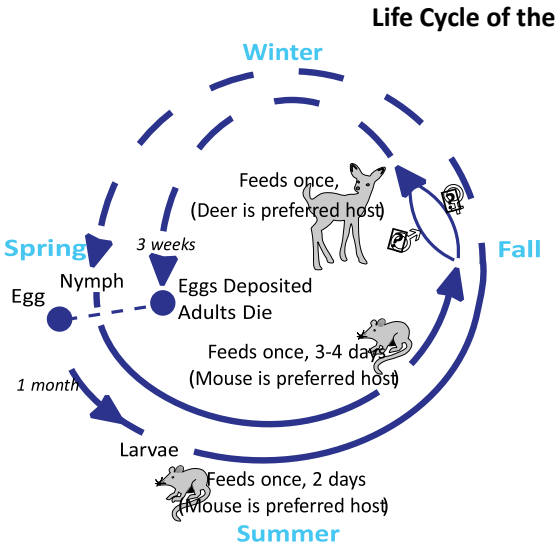
Lyme arthritis usually affects the knees.[33] In a minority of patients, arthritis can occur in other joints, including the ankles, elbows, wrists, hips, and shoulders. Pain is often mild or moderate, usually with swelling at the involved joint. Baker's cysts may form and rupture. In some cases, joint erosion occurs.

Acrodermatitis chronica atrophicans (ACA) is a chronic skin disorder observed primarily in Europe among the elderly.[23] ACA begins as a reddish-blue patch of discolored skin, often on the backs of the hands or feet. The lesion slowly atrophies over several weeks or months, with the skin becoming first thin and wrinkled and then, if untreated, completely dry and hairless.[34]

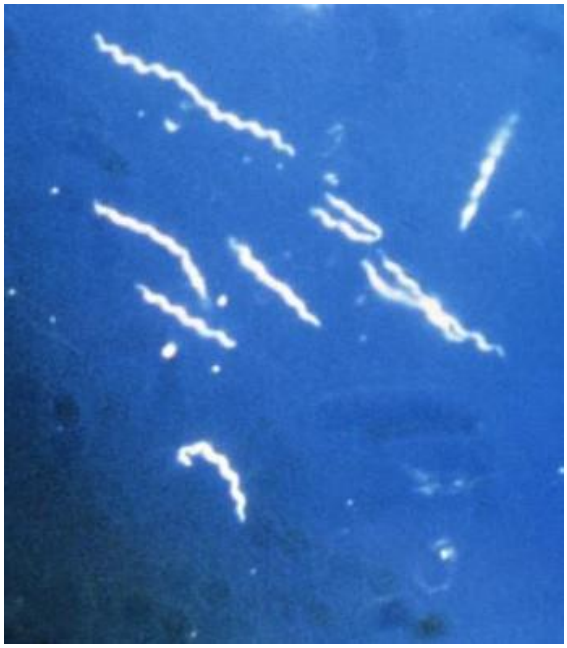
2 Cause

Main article: Lyme disease microbiology

Lyme disease is caused by spirochetal bacteria from the genus *Borrelia*. Spirochetes are surrounded by peptidoglycan and flagella, along with an outer membrane similar to other Gram-negative bacteria. Because of their double-membrane envelope, *Borrelia* bacteria are



Deer tick life cycle



Borrelia *bacteria, the causative agent of Lyme disease, magnified*

often mistakenly described as Gram negative despite the considerable differences in their envelope components from Gram-negative bacteria.[35] The Lyme-related *Borrelia* species are collectively known as *Borrelia burgdorferi sensu lato*, and show a great deal of genetic diversity.

B. burgdorferi sensu lato is made up of 18 closely related species, but only three clearly cause Lyme disease: *B. burgdorferi sensu stricto* (predominant in North America, but also present in Europe), *B. afzelii*, and *B. garinii* (both predominant in Eurasia).[36] Some studies have also proposed *B. bissettii* and *B. valaisiana* may sometimes infect humans, but these species do not seem to be important causes of disease.[37][38]

Ixodes scapularis*, the primary vector of Lyme disease in eastern North America*

Further information: Weather and climate effects on Lyme disease exposure

2.1 Transmission

Lyme disease is classified as a zoonosis, as it is transmitted to humans from a natural reservoir among rodents by ticks that feed on both sets of hosts.[39] Hardbodied ticks of the genus *Ixodes* are the main vectors of Lyme disease (also the vector for *Babesia*).[40] Most infections are caused by ticks in the nymphal stage, as they are very small and may feed for long periods of time undetected.[39] Larval ticks are very rarely infected.[41] Although deer are the preferred hosts of deer ticks, and the size of the tick population parallels that of the deer population, ticks cannot acquire Lyme disease spirochetes from deer. Rather, deer ticks acquire *Borrelia* microbes from infected rodents, such as the white-footed mouse, *Peromyscus leucopus*.[42]

Within the tick midgut, the *Borrelia*'s outer surface protein A (OspA) binds to the tick receptor for OspA, known as TROSPA. When the tick feeds, the *Borrelia* downregulates OspA and upregulates OspC, another surface protein. After the bacteria migrate from the midgut to the salivary glands, OspC binds to Salp15, a tick salivary protein that appears to have immunosuppressive effects that enhance infection.[43] Successful infection of the mammalian host depends on bacterial expression of OspC.[44]

Tick bites often go unnoticed because of the small size of the tick in its nymphal stage, as well as tick secretions that prevent the host from feeling any itch or pain from the bite. However, transmission is quite rare, with only about 1% of recognized tick bites resulting in Lyme disease. Transmission may occur within 24 hours of the tick bite.[45]

In Europe, the vector is *Ixodes ricinus*, which is also called the sheep tick or castor bean tick.[46] In China, *Ixodes 2 CAUSE*

persulcatus (the taiga tick) is probably the most important vector.[47] In North America, the black-legged tick or deer tick (*Ixodes scapularis*) is the main vector on the East Coast.[41]

The lone star tick (*Amblyomma americanum*), which is found throughout the Southeastern United States as far west as Texas, is unlikely to transmit the Lyme disease spirochetes,[48] though it may be implicated in a related syndrome called southern tick-associated rash illness, which resembles a mild form of Lyme disease.[49]

On the West Coast of the United States, the main vector is the western black-legged tick (*Ixodes pacificus*).[50] The tendency of this tick species to feed predominantly on host species such as lizards that are resistant to *Borrelia* infection appears to diminish transmission of Lyme disease in the West.[51][52]

Transmission across the placenta during pregnancy has not been demonstrated, and no consistent pattern of teratogenicity or specific "congenital Lyme borreliosis" has been identified. As with a number of other spirochetal diseases, adverse pregnancy outcomes are possible with untreated infection; prompt treatment with antibiotics reduces or eliminates this risk.[53][54]

While Lyme spirochetes have been found in insects, as well as ticks,[55] reports of actual infectious transmission appear to be rare.[56] Lyme spirochete DNA has been found in semen[57] and breast milk,[58] but transmission has not been known to take place through sexual contact.[59] According to the CDC, live spirochetes have not been found in breast milk, urine, or semen.[60] However, more recent studies published in 2014, suggest a link might exist.[61]

2.2 Tick-borne coinfections

Ticks that transmit *B. burgdorferi* to humans can also carry and transmit several other parasites, such as *Theileria microti* and *Anaplasma phagocytophilum*, which cause the diseases babesiosis and human granulocytic anaplasmosis (HGA), respectively.[62] Among early Lyme disease patients, depending on their location, 2–12% will also have HGA and 2–40% will have babesiosis.[63] Ticks in certain regions, including the lands along the eastern Baltic Sea, also transmit tickborne encephalitis.[64]

Coinfections complicate Lyme symptoms, especially diagnosis and treatment. It is possible for a tick to carry and transmit one of the coinfections and not *Borrelia*, making diagnosis difficult and often elusive. The Centers for Disease Control studied 100 ticks in rural New Jersey, and found 55% of the ticks were infected with at least one of
the pathogens.[65]

3.1 Immunological studies

3 Pathophysiology

B. burgdorferi can spread throughout the body during the course of the disease, and has been found in the skin, heart, joints, peripheral nervous system, and central nervous system.[44][66] Many of the signs and symptoms of Lyme disease are a consequence of the immune response to the spirochete in those tissues.[20]

B. burgdorferi is injected into the skin by the bite of an infected *Ixodes* tick. Tick saliva, which accompanies the spirochete into the skin during the feeding process, contains substances that disrupt the immune response at the site of the bite.[67] This provides a protective environment where the spirochete can establish infection. The spirochetes multiply and migrate outward within the dermis. The host inflammatory response to the bacteria in the skin causes the characteristic circular EM lesion.[44] Neutrophils, however, which are necessary to eliminate the spirochetes from the skin, fail to appear in the developing EM lesion. This allows the bacteria to survive and eventually spread throughout the body.[68]

Days to weeks following the tick bite, the spirochetes spread via the bloodstream to joints, heart, nervous system, and distant skin sites, where their presence gives rise to the variety of symptoms of disseminated disease. The spread of *B. burgdorferi* is aided by the attachment of the host protease plasmin to the surface of the spirochete.[69]

If untreated, the bacteria may persist in the body for months or even years, despite the production of *B. burgdorferi* antibodies by the immune system.[45] The spirochetes may avoid the immune response by decreasing expression of surface proteins that are targeted by antibodies, antigenic variation of the VlsE surface protein, inactivating key

immune components such as complement, and hiding in the extracellular matrix, which may interfere with the function of immune factors.[70][71]

In the brain, *B. burgdorferi* may induce astrocytes to undergo astrogliosis (proliferation followed by apoptosis), which may contribute to neurodysfunction.[72] The spirochetes may also induce host cells to secrete quinolinic acid, which stimulates the NMDA receptor on nerve cells, which may account for the fatigue and malaise observed with Lyme encephalopathy.[73] In addition, diffuse white matter pathology during Lyme encephalopathy may disrupt grey matter connections, and could account for deficits in attention, memory, visuospatial ability, complex cognition, and emotional status. White matter disease may have a greater potential for recovery than gray matter disease, perhaps because neuronal loss is less common. Resolution of MRI white matter hyperintensities after antibiotic treatment has been observed.[74]

Tryptophan, a precursor to serotonin, appears to be reduced within the central nervous system in a number of infectious diseases that affect the brain, including Lyme.[75] Researchers are investigating if this neurohormone secretion is the cause of neuropsychiatric disorders developing in some patients with borreliosis.[76]

3.1 Immunological studies

Exposure to the *Borrelia* bacterium during Lyme disease possibly causes a long-lived and damaging inflammatory response,[77] a form of pathogen-induced autoimmune disease.[78] The production of this reaction might be due to a form of molecular mimicry, where *Borrelia* avoids being killed by the immune system by resembling normal parts of the body's tissues.[79][80]

Chronic symptoms from an autoimmune reaction could explain why some symptoms persist even after the spirochetes have been eliminated from the body. This hypothesis may explain why chronic arthritis persists after antibiotic therapy, similar to rheumatic fever, but its wider application is controversial.[81][82]

3.2 Persistence

The National Institute of Health has supported research into bacterial resistance which has demonstrated persistence after antibiotic therapy in several animal models, including mice and primates. However, it was not possible to culture these bacteria and it is not known if they are infectious, or if they contribute to symptom persistence post-treatment.[83]

4 Diagnosis

Lyme disease is diagnosed clinically based on symptoms, objective physical findings (such as EM, facial palsy, or arthritis), or a history of possible exposure to infected ticks, as well as serological blood tests. The EM rash is not always a bull's eye, i.e., it can be solid red. When making a diagnosis of Lyme disease, health care providers should consider other diseases that may cause similar illnesses. Not all patients infected with Lyme disease develop the characteristic bull's-eye rash, and many may not recall a tick bite.[84]

Because of the difficulty in culturing *Borrelia* bacteria in the laboratory, diagnosis of Lyme disease is typically based on the clinical exam findings and a history of exposure to endemic Lyme areas.[40] The EM rash, which does not occur in all cases, is considered sufficient to establish a diagnosis of Lyme disease even when serologic blood tests are negative.[85][86] Serological testing can be used to support a clinically suspected case, but is not diagnostic by itself.[40]

Diagnosis of late-stage Lyme disease is often complicated by a multifaceted appearance and nonspecific symptoms, prompting one reviewer to call Lyme the new "great imitator".[87] Lyme disease may be misdiagnosed as multiple sclerosis, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, lupus, Crohn's disease, HIV, or other autoimmune and neurodegenerative diseases. As all patients with later-stage infection will have a positive antibody test, simple blood tests can exclude Lyme disease as a possible cause of the patients' symptoms.[88]

4.1 Laboratory testing

Several forms of laboratory testing for Lyme disease are available, some of which have not been adequately validated. The most widely used tests are serologies, which measure levels of specific antibodies in a patient's blood. These tests may be negative in early infection, as the body may not have produced a significant quantity of antibodies, but they are considered a reliable aid in the diagnosis of later stages of Lyme disease.[89] Serologic tests for Lyme disease are of limited use in people lacking objective signs of Lyme disease because of false positive results and cost.[90]

The serological laboratory tests most widely available and employed are the Western blot and ELISA. A twotiered protocol is recommended by the Centers for Disease Control and Prevention: the sensitive ELISA test is performed first, and if it is positive or equivocal, then the more specific Western blot is run.[91] The reliability of testing in diagnosis remains controversial.[40] Studies show the Western blot IgM has a specificity of 94– 96% for patients with clinical symptoms of early Lyme disease.[92][93] The initial ELISA test has a sensitivity of about 70%, and in two-tiered testing, the overall sensitivity is only 64%, although this rises to 100% in the subset of people with disseminated symptoms, such as
arthritis.[94]

Erroneous test results have been widely reported in both early and late stages of the disease, and can be caused by several factors, including antibody cross-reactions from other infections, including Epstein-Barr virus and cytomegalovirus,[95] as well as herpes simplex virus.[96]
The overall rate of false positives is low, only about 1 to 3%, in comparison to a false-negative rate of up to 36% in the early stages of infection using two-tiered testing.[94]

Polymerase chain reaction (PCR) tests for Lyme disease have also been developed to detect the genetic material (DNA) of the Lyme disease spirochete. PCR tests are susceptible to false positive results from poor laboratory technique.[97] Even when properly performed, PCR often shows false negative results with blood and cerebrospinal fluid specimens.[98] Hence, PCR is not widely performed for diagnosis of Lyme disease, but it may have a role in diagnosis of Lyme arthritis, because it is a highly sensitive way of detecting *ospA* DNA in synovial fluid.[99]

With the exception of culture or PCR, no practical means for detecting the presence of the organism is currently available, as serologic studies only test for antibodies of *Borrelia*. High titers of either immunoglobulin G (IgG)

or immunoglobulin M (IgM) antibodies to *Borrelia* antigens indicate disease, but lower titers can be misleading, because the IgM antibodies may remain after the initial infection, and IgG antibodies may remain for years.[100]

Western blot, ELISA, and PCR can be performed by either blood test via venipuncture or cerebrospinal fluid (CSF) via lumbar puncture. Though lumbar puncture is more definitive of diagnosis, antigen capture in the CSF is much more elusive; reportedly, CSF yields positive results in only 10–30% of patients cultured. The diagnosis of neurologic infection by *Borrelia* should not be excluded solely on the basis of normal routine CSF or negative CSF antibody analyses.[101]

New techniques for clinical testing of *Borrelia* infection have been developed, such as LTT-MELISA,[102] although the results of studies are contradictory, The first peer reviewed study assessing the diagnostic sensitivity and specificity of the test has been presented in 2012, showing potential for LTT to become a supportive diagnostic tool.[103] In 2014, research of LTT-MELISA concluded that it is "sensible" to include the LTT test in the diagnostic protocol for putative European-acquired Lyme borreliosis infections.[104] Others, such as focus floating microscopy, are under investigation.[105] New research indicates chemokine CXCL13 may also be a possible
marker for neuroborreliosis.[106]

Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. These tests include urine antigen tests, PCR tests on urine, immunofluorescent staining for cell wall-deficient forms of *B. burgdorferi*, and lymphocyte transformation tests. The CDC does not recommend these tests, and stated their use is "of great concern and is strongly discouraged".[98]

4.2 Imaging

Neuroimaging is controversial in whether it provides specific patterns unique to neuroborreliosis, but may aid in differential diagnosis and in understanding the pathophysiology of the disease.[107] Though controversial, some evidence shows certain neuroimaging tests can provide data that are helpful in the diagnosis of a patient. Magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) are two of the tests that can identify abnormalities in the brain of a patient affected with this disease. Neuroimaging findings in an MRI include lesions in the periventricular white matter, as well as enlarged ventricles and cortical atrophy. The findings are considered somewhat unexceptional because the lesions have been found to be reversible following antibiotic treatment. Images produced using SPECT show numerous areas where an insufficient amount of blood is being delivered the cortex and subcortical white matter. However, SPECT images are known to be not specific because they show a heterogeneous pattern in the

5.2 Vaccination

imaging. The abnormalities seen in the SPECT images are very similar to those seen in patients with cerebral vacuities and Creutzfeldt-Jakob disease, which makes them questionable.[108]

5 Prevention

Protective clothing includes a hat, long-sleeved shirt, and long trousers tucked into socks or boots. Light-colored clothing makes the tick more easily visible before it attaches itself. People should use special care in handling and allowing outdoor pets inside homes because they can bring ticks into the house.

Permethrin sprayed on clothing kills ticks on contact, and is sold for this purpose. Insect repellents with Picaridin, IR3535, DEET, or oil of lemon eucalyptus repel ticks, as well.[109]

A community can reduce the incidence of Lyme disease by reducing the numbers of primary hosts on which the deer tick depends, such as rodents, other small mammals, and deer. Reduction of the deer population may, over time, help break the reproductive cycle of the deer ticks and their ability to flourish in suburban and rural areas.[110]

5.1 Management of host animals

Lyme and all other deer tick-borne diseases can be prevented on a regional level by reducing the deer population on which the ticks depend for reproductive success. (Although deer ticks do acquire Lyme disease pathogens from rodents and not from deer, the size of the tick population tends to parallel that of the deer population.)[42] This has been demonstrated in the communities of Monhegan, Maine[111] and Mumford Cove, Connecticut.[112]

For example, in the U.S., reducing the deer population to levels of 8 to 10 per square mile (from the current levels of 60 or more deer per square mile in the areas of the country with the highest Lyme disease rates), the tick numbers can be brought down to levels too low to spread Lyme and other tick-borne diseases.[113] However, such a drastic reduction may be impractical in many areas. Routine veterinary control of ticks of domestic animals, including livestock, by use of chemical acaricides can contribute to reducing exposure of humans to ticks. However, the risk of acquiring Lyme disease does not depend on the existence of a local deer population, as is commonly assumed. Eliminating deer from smaller areas 2.5 ha (6.2 acres) may in fact lead to an increase in tick density and the rise of "tick-borne disease hotspots".[114]

Action can be taken to avoid getting bitten by ticks by using insect repellants, for example those that contain DEET. DEET-containing repellants are thought to be moderately effective in the prevention of tick bites.[115]

In Europe known reservoirs of *Borrelia burgdorferi* were 9 small mammals, 7 medium-sized mammals and 16 species of birds (including passerines, sea-birds and pheasants).[116] These animals seem to transmit spirochetes to ticks and thus participate in the natural circulation of B. burgdorferi in Europe. The house mouse is also suspected as well as other species of small rodents, particularly in Eastern Europe and Russia.[116] "The reservoir species that

contain the most pathogens are the European roe deer *Capreolus capreolus*;[117] "*it does not appear to serve as a major reservoir of B. burgdorferi*" thought Jaenson & al. (1992)[118] (incompetent host for *B. burgdorferi* and TBE virus) but it is important for feeding the ticks,[119] as red deer and wild boars (*Sus scrofa*),[120] in which one *Rickettsia* and three *Borrelia* species were identified",[117] with high risks of coinfection in roe deer.[121] Nevertheless, in the 2000s, in roe deer in Europe " *two species of Rickettsia and two species of Borrelia were identified*".[120]

5.2 Vaccination

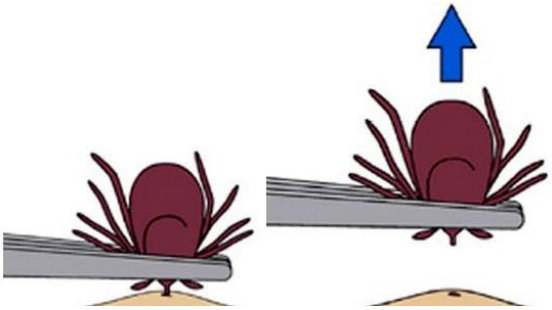
A recombinant vaccine against Lyme disease, based on the outer surface protein A (ospA) of *B. burgdorferi*, was developed by SmithKline Beecham. In clinical trials involving more than 10,000 people, the vaccine, called LYMErix, was found to confer protective immunity to *Borrelia* in 76% of adults and 100% of children with only mild or moderate and transient adverse effects.[122] LYMErix was approved on the basis of these trials by the Food and Drug Administration (FDA) on December 21, 1998.

Following approval of the vaccine, its entry in clinical practice was slow for a variety of reasons, including its cost, which was often not reimbursed by insurance companies.[123] Subsequently, hundreds of vaccine recipients reported they had developed autoimmune side effects. Supported by some patient advocacy groups, a number of class-action lawsuits were filed against GlaxoSmithKline, alleging the vaccine had caused these health problems. These claims were investigated by the FDA and the Centers for Disease Control, which found no connection between the vaccine and the autoimmune complaints.[124]

Despite the lack of evidence that the complaints were caused by the vaccine, sales plummeted and LYMErix was withdrawn from the U.S. market by GlaxoSmithKline in February 2002,[125] in the setting of negative media coverage and fears of vaccine side effects.[124][126] The fate of LYMErix was described in the medical literature as a "cautionary tale";[126] an editorial in *Nature* cited the withdrawal of LYMErix as an instance in which "unfounded public fears place pressures on vaccine developers that go beyond reasonable safety considerations."[127] The original developer of the OspA vaccine at the Max Planck Institute told *Nature*: "This just shows how irrational the world can be... There was no scientific justification for the first OspA vaccine LYMErix being pulled."[124]

New vaccines are being researched using outer surface protein C (OspC) and glycolipoprotein as methods of immunization.[128][129] Vaccines have been formulated and approved for prevention of Lyme disease in dogs. Currently, three Lyme disease vaccines are available. LymeVax, formulated by Fort Dodge Laboratories, contains intact dead spirochetes which expose the host to the organism. Galaxy Lyme, Intervet-Schering-Plough's vaccine, targets proteins OspC and OspA. The OspC antibodies kill any of the bacteria that have not been killed by the OspA antibodies. Canine Recombinant Lyme, formulated by Merial, generates antibodies against the OspA protein so a tick feeding on a vaccinated dog draws in blood full of anti-OspA antibodies, which kill the spirochetes in the tick's gut before they are transmitted to the dog.[130]

5.3 Tick removal



Removal of a tick using tweezers

Attached ticks should be removed promptly, as removal within 36 hours can reduce transmission rates.[131] Folk remedies for tick removal tend to be ineffective, offer no advantages in preventing the transfer of disease, and may

increase the risks of transmission or infection.[132] The best method is simply to pull the tick out with tweezers as close to the skin as possible, without twisting, and avoiding crushing the body of the tick or removing the head from the tick's body.[133] The risk of infection increases with the time the tick is attached, and if a tick is attached for less than 24 hours, infection is unlikely. However, since these ticks are very small, especially in the nymph stage, prompt detection is quite difficult.[131] The Australian Society of Clinical Immunology recommends against using tweezers to remove ticks but rather to kill the tick first by using a product to rapidly freeze the tick to prevent it from injecting more allergen-containing saliva. In a tick allergic person, the tick should be killed and removed in a safe place (e.g. an emergency department of a hospital).[134]

7 PROGNOSIS

5.4 Preventive antibiotics

The risk of infectious transmission increases with the duration of tick attachment.[135] It requires between 36 and 48 hours of attachment for the bacteria that causes Lyme to travel from within the tick into its saliva.[135] If a deer tick that is sufficiently likely to be carrying *Borrelia* is found attached to a person and removed, and if the tick has been attached for 36 hours or is engorged, a single dose of doxycycline administered within the 72 hours after removal may reduce the risk of Lyme disease. It is not generally recommended as development of infection is rare: about 50 people would have to be treated this way to prevent one case of infection.[1][135]

6 Treatment

Antibiotics are the primary treatment.[1][135] The specific approach to their use is dependent on the individual affected and the stage of the disease.[135] For most people with early localized infection, oral administration of doxycycline is widely recommended as the first choice, as it is effective against not only *Borrelia* bacteria but also a variety of other illnesses carried by ticks.[135] Doxycycline is contraindicated in children younger than eight years of age and women who are pregnant or breastfeeding;[135] alternatives to doxycycline are amoxicillin, cefuroxime axetil, and azithromycin.[135] Individuals with early disseminated or late infection may have symptomatic cardiac disease, refractory Lyme arthritis, or neurologic symptoms like meningitis or encephalitis.[135] Intravenous administration of ceftriaxone is recommended as the first choice in these cases;[135] cefotaxime and doxycycline are available as alternatives.[135]

These treatment regimens last from one to four weeks.[135] If joint swelling persists or returns, a second round of antibiotics may be considered.[135] Outside of that, a prolonged antibiotic regimen lasting more than 28 days is not recommended as no clinical evidence shows it to be effective.[135] IgM and IgG antibody levels may be elevated for years even after successful treatment with antibiotics.[135] As antibody levels are not indicative of treatment success, testing for them is not recommended.[135]

7 Prognosis

For early cases, prompt treatment is usually curative.[136] However, the severity and treatment of Lyme disease may be complicated due to late diagnosis, failure of antibiotic treatment, and simultaneous infection with other tick-borne diseases (coinfections), including ehrlichiosis, babesiosis, and immune suppression in the patient.

8.3 Europe

A meta-analysis published in 2005 found some patients with Lyme disease have fatigue, joint or muscle pain, and neurocognitive symptoms persisting for years, despite antibiotic treatment.[137] Patients with late stage Lyme disease have been shown to experience a level of physical disability equivalent to that seen in congestive heart failure.[138]

In dogs, a serious long-term prognosis may result in glomerular disease,[139] which is a category of kidney damage that may cause chronic kidney disease.[130] Dogs may also experience chronic joint disease if the disease is left untreated. However, the majority of cases of Lyme disease in dogs result in a complete recovery with, and

sometimes without, treatment with antibiotics.[140] In rare cases, Lyme disease can be fatal to both humans and dogs.[141]

8 Epidemiology

Countries with reported Lyme disease cases.

Lyme disease occurs regularly in Northern Hemisphere temperate regions.[142]

8.1 Africa

In northern Africa, *B. burgdorferi sensu lato* has been identified in Morocco, Algeria, Egypt and Tunisia.[143][144][145]

Lyme disease in sub-Saharan Africa is presently unknown, but evidence indicates it may occur in humans in this region. The abundance of hosts and tick vectors would favor the establishment of Lyme infection in Africa.[146] In East Africa, two cases of Lyme disease have been reported in Kenya.[147]

8.2 Asia

B. burgdorferi sensu lato-infested ticks are being found more frequently in Japan, as well as in northwest China, Nepal, Thailand and far eastern Russia.[148][149] *Borrelia* has also been isolated in Mongolia.[150]

8.3 Europe

In Europe, Lyme disease is caused by infection with one or more pathogenic European genospecies of the spirochaete *B. burgdorferi sensu lato*, mainly transmitted by the tick *Ixodes ricinus*.[151] Cases of *B. burgdorferi sensu lato*-infected ticks are found predominantly in central Europe, particularly in Slovenia and Austria, but have been isolated in almost every country on the continent.[152] Incidence in southern Europe, such as Italy and Portugal, is much lower.[153]

8.3.1 United Kingdom

In the United Kingdom the number of laboratory confirmed cases of Lyme disease has been rising steadily since voluntary reporting was introduced in 1986[154] when 68 cases were recorded in the UK and Republic of Ireland combined.[155] In the UK there were 23 confirmed cases in 1988 and 19 in 1990,[156] but 973 in 2009[154] and 953 in 2010.[157] Provisional figures for the first 3 quarters of 2011 show a 26% increase on the same period in 2010.[158]

It is thought, however, that the actual number of cases is significantly higher than suggested by the above figures, with the UK's Health Protection Agency estimating that there are between 2,000 and 3,000 cases per year,[157] (with an average of around 15% of the infections acquired overseas[154]), while Dr Darrel Ho-Yen, Director of the Scottish Toxoplasma Reference Laboratory and National Lyme Disease Testing Service, believes that the number of confirmed cases should be multiplied by 10 "to take account of wrongly diagnosed cases, tests giving false results,

sufferers who weren't tested, people who are infected but not showing symptoms, failures to notify and infected individuals who don't consult a doctor."[159][160]

Despite Lyme disease (Borrelia burgdorferi infection) being a notifiable disease in Scotland[161] since January 1990[162] which should therefore be reported on the basis of clinical suspicion, it is believed that many GPs are unaware of the requirement.[163] Mandatory reporting, limited to laboratory test results only, was introduced throughout the UK in October 2010, under the Health Protection (Notification) Regulations 2010.[154]

Although there is a greater incidence of Lyme disease in the New Forest, Salisbury Plain, Exmoor, the South Downs, parts of Wiltshire and Berkshire, Thetford Forest[164] and the West coast and islands of Scotland[165] infected ticks are widespread, and can even be found in the parks of London.[156][166] A 1989 report found that 25% of forestry workers in the New Forest were seropositive, as were between 2% and 4-5% of the general local population of the area.[167][168]

Tests on pet dogs, carried out throughout the country in 2009 indicated that around 2.5% of ticks in the UK may be infected, considerably higher than previously lead to an increase in tick activity in the future, as well as an increase

thought.[169][170] It is thought that global warming may in the amount of time that people spend in public parks, thus increasing the risk of infection.[171]

8.4 North America

Many studies in North America have examined ecological and environmental correlates of Lyme disease prevalence. A 2005 study using climate suitability modelling of *I. scapularis* projected that climate change would cause an overall 213% increase in suitable vector habitat by the year 2080, with northward expansions in Canada, increased suitability in the central U.S., and decreased suitable habitat and vector retraction in the southern U.S.[172] A 2008 review of published studies concluded that the presence of forests or forested areas was the only variable that consistently elevated the risk of Lyme disease, and that other environmental variables showed little or no concordance between studies.[173] The authors argued that the factors influencing tick density and human risk between sites are still poorly understood, and that future studies should be conducted over longer time periods, become more standardized across regions, and incorporate existing knowledge of regional Lyme disease ecology.[173]

8.4.1 Canada

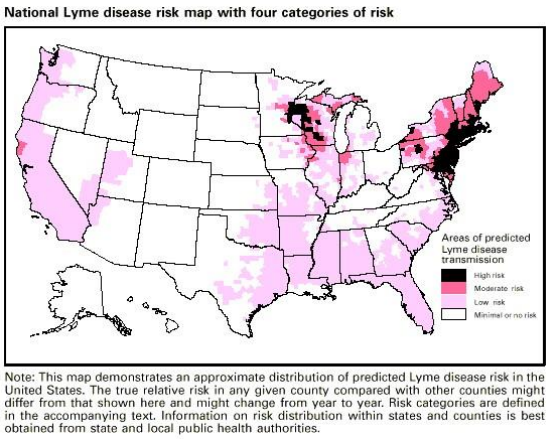
Owing to changing climate, the range of ticks able to carry Lyme disease has expanded from a limited area of Ontario to include areas of southern Quebec, Manitoba, northern Ontario, southern New Brunswick, south-west Nova Scotia and limited parts of Saskatchewan and Alberta, as well as British Columbia.
Cases have been reported as far east as the island of Newfoundland.[174][175][176] A model-based prediction by Leighton *et al.* (2012) suggests that the range of the *I. scapularis* tick will expand into Canada by 46 km/year over the next decade, with warming climatic temperatures as the main driver of increased speed of spread.[177]

8.4.2 Mexico

A 2007 study suggests *Borrelia burgdorferi* infections are endemic to Mexico, from four cases reported between 1999 and 2000.[178]

8.4.3 United States

Each year, approximately 30,000 new cases are reported to the CDC however, this number is likely underestimated. The CDC is currently conducting research on evaluation and diagnostics of the disease and preliminary results suggest the number of new cases to be around 300,000.[179]



CDC map showing the risk of Lyme disease in the United States, particularly its concentration in the Northeast Megalopolis and western Wisconsin.

Lyme disease is the most common tick-borne disease in North America and Europe, and one of the fastestgrowing infectious diseases in the United States. Of cases reported to the United States CDC, the ratio of Lyme disease infection is 7.9 cases for every 100,000 persons. In the ten states where Lyme disease is most common, the average was 31.6 cases for every 100,000 persons for the year 2005.[180][181][182]

Although Lyme disease has been reported in all states except Montana,[183] about 99% of all reported cases are confined to just five geographic areas (New England, Mid-Atlantic, East-North Central, South Atlantic, and West North-Central).[184] New 2011 CDC Lyme case definition guidelines are used to determine confirmed CDC surveillance cases.[185]

Effective January 2008, the CDC gives equal weight to laboratory evidence from 1) a positive culture for *B. burgdorferi*; 2) two-tier testing (ELISA screening and Western blot confirming); or 3) single-tier IgG (old infection) Western blot.[186] Previously, the CDC only included laboratory evidence based on (1) and (2) in their surveillance case definition. The case definition now includes the use of Western blot without prior ELISA screen.[186]

The number of reported cases of the disease has been increasing, as are endemic regions in North America. For example, *B. burgdorferi sensu lato* was previously thought to be hindered in its ability to be maintained in an enzootic cycle in California, because it was assumed the large lizard population would dilute the prevalence of *B. burgdorferi* in local tick populations; this has since been brought into question, as some evidence has suggested lizards can become infected.[187]

Except for one study in Europe,[188] much of the data implicating lizards is based on DNA detection of the spirochete and has not demonstrated lizards are able to infect ticks feeding upon them.[187][189][190][191] As some experiments suggest lizards are refractory to infection with *Borrelia*, it appears likely their involvement in the enzootic cycle is more complex and species-specific.[52]

While *B. burgdorferi* is most associated with ticks hosted by white-tailed deer and white-footed mice, *Borrelia afzelii* is most frequently detected in rodent-feeding vector ticks, and *Borrelia garinii* and *Borrelia valaisiana* appear to be associated with birds. Both rodents and birds are competent reservoir hosts for *B. burgdorferi sensu stricto*. The resistance of a genospecies of Lyme disease spirochetes to the bacteriolytic activities of the alternative complement pathway of various host species may determine its reservoir host association.

Several similar but apparently distinct conditions may exist, caused by various species or subspecies of *Borrelia* in North America. A regionally restricted condition that may be related to *Borrelia* infection is southern tick-associated rash illness (STARI), also known as Masters' disease. *Amblyomma americanum*, known commonly as the lone-star tick, is recognized as the primary vector for STARI. In some parts of the geographical distribution of STARI, Lyme disease is quite rare (e.g., Arkansas), so patients in these regions experiencing Lyme-like symptoms—especially if they follow a bite from a lone-star tick—should consider STARI as a possibility. It is generally a milder condition than Lyme and typically responds well to antibiotic treatment.

Although Montana is the only state that has not reported a confirmed case of Lyme disease, in recent years there have been 5 to 10 cases a year of a disease similar to Lyme. It occurs primarily in pockets along the Yellowstone

River in central Montana. People have developed a red bull's-eye rash around a tick bite followed by weeks of fatigue and a fever.[183]

Lyme disease prevalence is comparable among males and females. A wide range of age groups is affected, though the number of cases is highest among 10–19-year-olds. For unknown reasons, Lyme disease is seven times more common among Asians.[192]

8.5 South America

In South America, tick-borne disease recognition and occurrence is rising. In Brazil, a Lyme-like disease known as Baggio–Yoshinari syndrome was identified, caused by microorganisms that do not belong to the *B. burgdorferi sensu lato* complex and transmitted by ticks of the *Amblyomma* and *Rhipicephalus* genera.[193] The first reported case of BYS in Brazil was made in 1992 in Cotia, São Paulo.[194] *B. burgdorferi sensu stricto* antigens in patients have been identified in Colombia and Bolivia.

9 History

The evolutionary history of *Borrelia burgdorferi* genetics has been the subject of recent studies. One study has found that prior to the reforestation that accompanied post colonial farm abandonment in New England and the wholesale migration into the mid-west that occurred during the early 19th century, Lyme disease was present for thousands of years in America and had spread along with its tick hosts from the Northeast to the Midwest.[195]

John Josselyn, who visited New England in 1638 and again from 1663–1670, wrote "there be infinite numbers of tikes hanging upon the bushes in summer time that will cleave to man's garments and creep into his breeches eating themselves in a short time into the very flesh of a man. I have seen the stockins of those that have gone through the woods covered with them."[196]

This is also confirmed by the writings of Peter Kalm, a Swedish botanist who was sent to America by Linnaeus, and who found the forests of New York "abound" with ticks when he visited in 1749. When Kalm's journey was retraced 100 years later, the forests were gone and the Lyme bacterium had probably become isolated to a few pockets along the northeast coast, Wisconsin, and Minnesota.[197]

Perhaps the first detailed description of what is now known as Lyme disease appeared in the writings of Reverend Dr John Walker after a visit to the Island of Jura
(Deer Island) off the west coast of Scotland in 1764.[198] He gives a good description both of the symptoms of Lyme disease (with "exquisite pain [in] the interior parts of the limbs") and of the tick vector itself, which he describes as a "worm" with a body which is "of a reddish colour and of a compressed shape with a row of feet on each side" that "penetrates the skin". Many people from this area of Great Britain immigrated to North America between 1717 and the end of the 18th century.

The examination of preserved museum specimens has found *Borrelia* DNA in an infected *Ixodes ricinus* tick from Germany that dates back to 1884, and from an infected mouse from Cape Cod that died in 1894.[197] The 2010 autopsy of Ötzi the Iceman, a 5,300-year-old mummy, revealed the presence of the DNA sequence of *Borrelia burgdorferi* making him the earliest known human with Lyme disease.[199]

The early European studies of what is now known as Lyme disease described its skin manifestations. The first study dates to 1883 in Breslau, Germany (now Wrocław, Poland), where physician Alfred Buchwald described a man who had suffered for 16 years with a degenerative skin disorder now known as acrodermatitis chronica atrophicans.[200]

9.1 20th century

At a 1909 research conference, Swedish dermatologist Arvid Afzelius presented a study about an expanding, ring-like lesion he had observed in an older woman following the bite of a sheep tick. He named the lesion *erythema migrans*.[200] The skin condition now known as borrelial lymphocytoma was first described in 1911.[201]

Neurological problems following tick bites were recognized starting in the 1920s. French physicians Garin and Bujadoux described a farmer with a painful sensory radiculitis accompanied by mild meningitis following a tick bite. A large, ring-shaped rash was also noted, although the doctors did not relate it to the meningoradiculitis. In 1930, the Swedish dermatologist Sven Hellerström was the first to propose EM and neurological symptoms following a tick bite were related.[202] In the 1940s, German neurologist Alfred Bannwarth described several cases of chronic lymphocytic meningitis and polyradiculoneuritis, some of which were accompanied by erythematous skin lesions.

Carl Lennhoff, who worked at the Karolinska Institute in Sweden, believed many skin conditions were caused by spirochetes. In 1948, he used a special stain to microscopically observe what he believed were spirochetes in various types of skin lesions, including EM.[203] Although his conclusions were later shown to be erroneous, interest in the study of spirochetes was sparked. In 1949, Nils Thyresson, who also worked at the Karolinska Institute, was the first to treat ACA with penicillin.[204] In the 1950s, the relationship among tick bite, lymphocytoma, EM and Bannwarth's syndrome was recognized throughout Europe leading to the widespread use of penicillin for treatment in Europe.[205][206]

In 1970, a dermatologist in Wisconsin named Rudolph Scrimenti recognized an EM lesion in a patient after recalling a paper by Hellerström that had been reprinted in an American science journal in 1950. This was the first documented case of EM in the United States. Based on the European literature, he treated the patient with penicillin.[207]

The full syndrome now known as Lyme disease was not recognized until a cluster of cases originally thought to be juvenile rheumatoid arthritis was identified in three towns in southeastern Connecticut in 1975, including the towns Lyme and Old Lyme, which gave the disease its popular name.[208] This was investigated by physicians David Snydman and Allen Steere of the Epidemic Intelligence Service, and by others from Yale University, including Dr. Stephen Malawista, who is credited as a co-discover of the disease.[209] The recognition that the patients in the United States had EM led to the recognition that "Lyme arthritis" was one manifestation of the same tick-borne condition known in Europe.[210]

Before 1976, elements of *B. burgdorferi sensu lato* infection were called or known as tick-borne meningopolyneu

ritis, Garin-Bujadoux syndrome, Bannwarth syndrome, Afzelius' disease,[211] Montauk Knee or sheep tick fever. Since 1976 the disease is most often referred to as Lyme disease,[212][213] Lyme borreliosis or simply borreliosis.

In 1980, Steere, *et al.*, began to test antibiotic regimens in adult patients with Lyme disease.[214] In the same year, New York State Health Dept. epidemiologist Jorge Benach provided Willy Burgdorfer, a researcher at the Rocky Mountain Biological Laboratory, with collections of *I. dammini* [*scapularis*] from Shelter Island, NY, a known Lyme-endemic area as part of an ongoing investigation of Rocky Mountain spotted fever. In examining the ticks for rickettsiae, Burgdorfer noticed "poorly stained, rather long, irregularly coiled spirochetes." Further examination revealed spirochetes in 60% of the ticks. Burgdorfer credited his familiarity with the European literature for his realization that the spirochetes might be the "long-sought cause of ECM and Lyme disease." Benach supplied him with more ticks from Shelter Island and sera from patients diagnosed with Lyme disease. University of Texas Health Science Center researcher Alan Barbour "offered his expertise to culture and immunochemically characterize the organism." Burgdorfer subsequently confirmed his discovery by isolating, from patients with Lyme disease, spirochetes identical to those found in ticks.[215] In June 1982, he published his findings in Science, and the spirochete was named *Borrelia burgdorferi* in his honor.[216]

After the identification of *B. burgdorferi* as the causative agent of Lyme disease, antibiotics were selected for testing, guided by *in vitro* antibiotic sensitivities, including tetracycline antibiotics, amoxicillin, cefuroxime axetil, intravenous and intramuscular penicillin and intravenous ceftriaxone.[217][218] The mechanism of tick transmission was also the subject of much discussion. *B. burgdorferi* spirochetes were identified in tick saliva in 1987, confirming the hypothesis that transmission occurred via tick salivary glands.[219]

Jonathan Edlow, Professor of Medicine at Harvard Medical School, quotes the late Ed Masters (discoverer of STARI, a Lyme-like illness) in his book *Bull's-Eye*, on the history of Lyme disease. Edlow writes:

> Masters points out that the "track record" of the "conventional wisdom" regarding Lyme disease is not very good: "First off, they said it was a new disease, which it wasn't. Then it was thought to be viral, but it isn't. Then it was thought that sero-negativity didn't exist, which it does. They thought it was easily treated by short courses of antibiotics, which sometimes it isn't. Then it was only the *Ixodes dammini* tick, which we now know is not even a separate valid tick species. If you look throughout the history, almost every time a major dogmatic statement has been made about what we 'know' about this disease, it was subsequently proven wrong or underwent major modifications."[220]

10 Society and culture

Urbanization and other anthropogenic factors can be implicated in the spread of Lyme disease to humans. In many areas, expansion of suburban neighborhoods has led to gradual deforestation of surrounding wooded areas and increased border contact between humans and tickdense areas. Human expansion has also resulted in reduction of predators that hunt deer as well as mice, chipmunks and other small rodents—the primary reservoirs for Lyme disease. As a consequence of increased human contact with host and vector, the likelihood of transmission of the disease has greatly increased.[221][222] Researchers are investigating possible links between global warming and the spread of vector-borne diseases, including Lyme disease.[223]

10.1 Controversyoverterm"chronicLyme disease"

Main article: Lyme disease controversy

The term "chronic Lyme disease" is controversial and not recognized in the medical literature,[224] and most medical authorities advise against long-term antibiotic treatment for Lyme disease.[90][225][226] Studies have shown that most patients diagnosed with "chronic Lyme disease" either have no objective evidence of previous or current infection with *B. burgdorferi* or are patients who should be classified as having post-treatment Lyme disease syndrome (PTLDS), which is defined as continuing or relapsing non-specific symptoms (such as fatigue, musculoskeletal pain, and cognitive complaints) in a patient previously treated for Lyme disease.[227]

11 Other animals

Prevention of Lyme disease is an important step in keeping dogs safe in endemic areas. Prevention education and a number of preventative measures are available. First, for dog owners who live near or who often frequent tickinfested areas, routine vaccinations of their dogs is an important step.[228]

Another crucial preventive measure is the use of persistent acaricides, such as topical repellents or pesticides that contain triazapentadienes (Amitraz), phenylpyrazoles (Fipronil), or permethrin (pyrethroids).[229] These acaricides target primarily the adult stages of Lymecarrying ticks and reduce the number of reproductively active ticks in the environment.[228] Formulations of these ingredients are available in a variety of topical forms, including spot-ons, sprays, powders, impregnated collars, solutions, and shampoos.[229]

Examination of a dog for ticks after being in a tickinfested area is an important precautionary measure to take in the prevention of Lyme disease. Key spots to examine include the head, neck, and ears.[230]